Prevention of pediatric asthma and allergy
- with special reference to probiotics
Dubai 7.12.2010

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Primary prevention- for whom?

- Most of the intervention studies have targeted high-risk groups, for obvious reasons BUT
- who are the true ”high-risk groups” now that 40% of the mothers and fathers are atopic?
- no genetic markers available yet, umbilical cord blood does not give promising results in targeting...
Table 1. Primary prevention measures /WAO 2004 (Johansson SGO, Hahtela T, eds.)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Category of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Smoking and exposure to environmental tobacco smoke should be avoided, particularly during pregnancy and early childhood.</td>
<td>B</td>
</tr>
<tr>
<td>Tobacco smoke should be removed from workplaces.</td>
<td>B</td>
</tr>
<tr>
<td>2) Damp housing conditions should be avoided, and indoor air pollutants should be reduced.</td>
<td>C</td>
</tr>
<tr>
<td>3) Breast-feeding should be continued until 4-6-months.</td>
<td>B</td>
</tr>
<tr>
<td>No special diet is needed for the lactating mother.</td>
<td>A</td>
</tr>
<tr>
<td>4) In high-risk children, exposure to inhalant allergens should be reduced.</td>
<td>B</td>
</tr>
<tr>
<td>Note: the most recent data, however, indicate that even high-risk children may develop tolerance against allergens; the dose-response curve appears to be bell-shaped [3,18].</td>
<td></td>
</tr>
<tr>
<td>5) Highly irritant agents in occupational settings should be avoided.</td>
<td>C</td>
</tr>
<tr>
<td>In the case this is not possible, measures to prevent employee exposure should be implemented.</td>
<td></td>
</tr>
</tbody>
</table>
Present exposure to cat allergens and sensitization to cat (Custovic A. JACI 2001)

**Bell-shaped sensitization curve:**

Heavy exposure induces tolerance, because of strong Treg function!
<table>
<thead>
<tr>
<th>Measure</th>
<th>Category of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Atopic eczema in infants and children should be treated to prevent respiratory allergy.</td>
<td>D</td>
</tr>
<tr>
<td>2) Upper respiratory disease (rhinoconjunctivitis) should be treated to reduce risk of development of asthma.</td>
<td>D</td>
</tr>
<tr>
<td>3) In young children already sensitised to indoor allergens, exposure should be reduced to prevent onset of allergic disease.</td>
<td>B</td>
</tr>
<tr>
<td>4) Employees should be removed from occupational exposure if they have developed symptoms associated with occupational allergic sensitization.</td>
<td>C</td>
</tr>
</tbody>
</table>
Probiotics – are they useful?

Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: A randomized, double-blind, placebo-controlled trial

Kaarina Kukkonen, MD,a Erkki Savilahti, MD, PhD,b Tari Haahtela, MD, PhD,a Kaisu Juntunen-Backman, MD, PhD,a Riitta Korpela, PhD,c,d Tuija Poussa, MSc,e Tuula Tuure, PhD,d and Mikael Kuitunen, MD, PhDa Helsinki and Tampere, Finland

Editors’ choice articles

Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort

Mikael Kuitunen, MD, PhD,a Kaarina Kukkonen, MD,a Kaisu Juntunen-Backman, MD, PhD,a Riitta Korpela, PhD,c,d Tuija Poussa,e Tuula Tuure, PhD,d Tari Haahtela, MD, PhD,a and Erkki Savilahti, MD, PhDb Helsinki and Tampere, Finland

JACI 2007

JACI 2009
Protocol

- RCT double-blind
- High-risk families
- Treatment group
  - Mothers: caps 2x/day 4 w before delivery
  - Infants: 1 caps+GOS 6 mo
- Placebo
  - Mothers: inert cellulose caps
  - Infants placebo caps+gtt
- No dietary manipulation

- Lactobacillus rhamnosus GG (ATCC 53103) $5 \times 10^9$
- L. rhamnosus Lc705 $5 \times 10^9$
- Bifidobacterium breve 99 (DSM 13692) $2 \times 10^8$
- Propionibact. freudenreichii ssp. shermanii JS $2 \times 10^9$
- galacto-oligosaccharide (GOS) 0.8g
Randomized 1223

mothers: probiotic
610

infants:
ITT 506

2 y follow-up 461

5 y follow-up 445

mothers: placebo
613

infants:
ITT 512

2 y follow-up 464

5 y follow-up 446

exclusion: prematurity <37w, B-twin, major malformations

91%

88%
Probiotics prevented eczema and other allergic manifestations associated with IgE but not overall allergic diseases.

Kukkonen et al JACI 2007;119:192
<table>
<thead>
<tr>
<th>Study</th>
<th>Interv</th>
<th>N</th>
<th>age</th>
<th>PR v. PI eczema%</th>
<th>OR 95%CI</th>
<th>IgE+eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalliomäki 2001, 2003, 2007</td>
<td>1+6m</td>
<td>159</td>
<td>2</td>
<td>23 vs. 46</td>
<td>0.36 (0.17-0.77)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>108</td>
<td></td>
<td>4</td>
<td>26 vs. 46</td>
<td>0.42 (0.18-0.94)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>115</td>
<td></td>
<td>7</td>
<td>43 vs. 66</td>
<td>0.58 (0.35-0.94)</td>
<td></td>
</tr>
<tr>
<td>Kukkonen 2007, Kuitunen 2009</td>
<td>1+6m</td>
<td>925</td>
<td>2</td>
<td>26 vs. 32</td>
<td>0.74 (0.55-0.98)</td>
<td>0.66 (0.46-0.95)</td>
</tr>
<tr>
<td></td>
<td>891</td>
<td></td>
<td>5</td>
<td>39 vs. 43</td>
<td>0.85 (0.65-1.11)</td>
<td></td>
</tr>
<tr>
<td>Taylor 2007</td>
<td>+6m</td>
<td>177</td>
<td>1</td>
<td>43 vs. 39</td>
<td>1.18 (0.64-2.16)</td>
<td>2.18 (1.01-4.72)</td>
</tr>
<tr>
<td>Abrahamson07</td>
<td>1m+1y</td>
<td>188</td>
<td>2</td>
<td>35 vs. 34</td>
<td>1.06 (0.58-1.93)</td>
<td>0.53 (0.24-1.16)</td>
</tr>
<tr>
<td>Kopp 2008</td>
<td>1+6m</td>
<td>94</td>
<td>2</td>
<td>28 vs. 27</td>
<td>1.04 (0.42-2.57)</td>
<td></td>
</tr>
<tr>
<td>Wickens 2008</td>
<td>1m+2y</td>
<td>446</td>
<td>2</td>
<td>15 vs. 27</td>
<td>0.51 (0.3-0.85)</td>
<td>0.51 (0.27-0.87)</td>
</tr>
<tr>
<td>Soh 2008</td>
<td>+6m</td>
<td>245</td>
<td>1</td>
<td>22 vs. 25</td>
<td>0.82 (0.44-1.52)</td>
<td>1.08 (0.44-2.65)</td>
</tr>
<tr>
<td>West 2009</td>
<td>+4-13m</td>
<td>171</td>
<td>1</td>
<td>11 vs. 22</td>
<td>NNT 9</td>
<td></td>
</tr>
<tr>
<td>Niers 2009</td>
<td>1+12m</td>
<td>98</td>
<td>1</td>
<td>12 vs. 29</td>
<td>NNT 6</td>
<td></td>
</tr>
<tr>
<td>Dotterud 2010</td>
<td>1+6m,ä</td>
<td>278</td>
<td>2</td>
<td></td>
<td>0.51 (0.3-0.87)</td>
<td></td>
</tr>
<tr>
<td>Kim 2010</td>
<td>1+6m,ä</td>
<td>112</td>
<td>2</td>
<td>36 vs.63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Safety

No of complaints

- No side-effects
- No effect on growth
- Less respiratory infections (6-24 mo)
- Less antibiotics (0-6 kk)

Kukkonen et al JACI 2007; Pediatr Allerg Immunol 2006; Pediatrics 2008
5 year follow-up – is any effect left?

Kuitunen et al JACI 2009
Cesarean section – 16% of children

Kuitunen et al JACI 2009
Prevent a high-grade inflammation with a low-grade one!


Stimulating innate immunity with probiotics mimic inflammation caused by helminths

Treatment and IL-10

CRP (µg/mL)

* p=0.021

Before

After

Infants with eczema

LGG (47) MIX (38) Placebo (36)

P=0.016

0.0 0.5 1.0 1.5

0.0

1.0

1.5

P=0.016

Before

After

LGG N=31 MIX N=21 Placebo N=26

CRP (µg/mL)

0.0 0.5 1.0 1.5

0.0 1.0 2.0 3.0

0.0

1.0

2.0

3.0

0.0
Plasma total IgA and IgE

→ probiotic-triggered increase in IL-10 and total IgE without specific-IgE change

Marschan et al. Clin Exp Allergy 2008;38
Chronic low-grade inflammation is protecting?

Stimulating innate immunity with probiotics mimic inflammation caused by helminths

- Probiotics: induce CRP
- Placebo: non-allergic children had higher CRP
- Low CRP production = marker of poor inflammatory pressure and a risk factor for eczema

Helminth infection
- Helminth infections may protect against allergy
- Increase in IgE and IL-10 is associated with regulatory mechanisms, such as TGFβ
- Antihelminth treatment of infected children result in increased atopic reactivity, but protection is not permanent and requires continuous stimulation
- Probiotics should be given on a continuous basis?
It is obvious that we are loosing protective factors and not so much exposed to new risk factors.
The Karelia Allergy Study - comparison of the Finnish and Russian Karelia

Laatikainen T, et al. 2010, Allergy, in press
Table 3. Endorsement of immunological tolerance

<table>
<thead>
<tr>
<th>UNSPECIFIC WAYS TO AFFECT INNATE IMMUNITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Living on a farm</td>
</tr>
<tr>
<td>➢ Adherence to anthroposophic lifestyle (eg. organic food)</td>
</tr>
<tr>
<td>➢ Use of probiotics</td>
</tr>
<tr>
<td>➢ Use of other bacteria-containing (fermented) products*</td>
</tr>
<tr>
<td>➢ Consumption of fresh fruit and vegetables</td>
</tr>
<tr>
<td>➢ Consumption of farm milk</td>
</tr>
<tr>
<td>➢ Consumption of kefir*</td>
</tr>
<tr>
<td>➢ Consumption of healthy diet (Mediterranean, Baltic)</td>
</tr>
<tr>
<td>➢ Spending time in nature, outdoor physical activities</td>
</tr>
</tbody>
</table>

* efficacy not yet proven in humans
Finnish Allergy Programme 2008-2018

- Reduce allergy burden. Endorse health, not allergy.
- Strengthen tolerance. Avoid allergens only if mandatory
- In severe allergy, recognize and treat early. Prevent exacerbations.
- Improve air quality. Stop smoking

Old model of atopy prevention
Fanni 1 year 2010

New model!
How does it work?

- Dendritic cells extend to gut lumen
- They bear receptors for conserved molecular bacterial patterns
  - TLR4 for LPS etc; TLR2 for Gram+
- Stimulation results in change in cytokine balance
  - shown in treatment and prevention of atopic diseases

Gómez-Llorente et al ProcNutrSoc2010;1-9
Seuranta & lopputulos

- Kumulatiivinen prevalenssi 2v
  - ekseema
  - allerginen nuha
  - astma
  - ruoka-allergia
- Herkistyminen 2v
  - prick testi +
    - 8 allergeneenia
  - spesifi IgE
    - 6 allergeneenia, > 0.7kU/L

- Seurantatutk 6 kk, 2 ja 5 v
- vapaa pääsy pediatrille
CRP, IL-10 in 6mo plasma of 98 infants

WAO Allergy Plan -suggestion

- Reduce allergy burden. Endorse health, not allergy.
- In mild allergy, strengthen tolerance. Avoid allergens only if mandatory
- In severe allergy, recognize and treat early. Prevent exacerbations. Strengthen tolerance
- Improve air quality. Stop smoking